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**Box No. I TITLE OF INVENTION**
Methods and compositions for improved therapies using gonadotropin hormone releasing hormone compositions

**Box No. II APPLICANT** ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Debiopharm S.A.
17, Rue des Terreaux
Case Postale 211
1000 Lausanne 9 / Switzerland

Telephone No. +4121 3210111
Facsimile No. +4121 3210169
Teleprinter No.
Applicant's registration No. with the Office

State *(that is, country)* of nationality: Switzerland
State *(that is, country)* of residence: Switzerland

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Denis Génin
Debiopharm S.A.
17, Rue des Terreaux
Case Postale 211
1000 Lausanne 9 / Switzerland

Telephone No. +4121 3210111
Facsimile No. +4121 3210169
Teleprinter No.
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| drawings | : | 0 |
| **Sub-total number of sheets** | : | 24 |
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# METHODS AND COMPOSITIONS FOR IMPROVED THERAPIES USING GONADOTROPIN HORMONE RELEASING HORMONE COMPOSITIONS

## BACKGROUND AND PRIOR ART

Gonadotropin hormone releasing hormone (GnRH) agonists and antagonists have been used to treat benign gynecological disorders including premenstrual syndrome and androgen-dependent cancer of the prostate. GnRH is also known as luteinizing hormone releasing hormone. GnRH is secreted by the hypothalamus in the pituitary portal system in a pulsating fashion. Because the hormone has a half life of the order of minutes, the pituitary gland is exposed to pulses of hormone. This exposure results in the secretion of the gonadotropins, i.e., luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men LH acts on the Leydig cells of the testes, stimulating the secretion of testosterone. FSH is responsible for spermatogenesis. Testosterone appears to feedback-inhibit secretion of GnRH and reduce the sensitivity of the pituitary to the hormone. In women FSH acts on the ovaries, stimulating secretion of estrogen. The main functions of LH in women are to support follicular maturation and to trigger ovulation at mid-follicular cycle. Like testosterone, estrogen appears to be capable of feedback inhibition of GnRH secretion and action.

Administration of potent agonists of GnRH was found to cause an initial flare-up of LH and FSH release that is followed by a complete down-regulation of GnRH receptor in the pituitary. As a consequence, LH and FSH are no longer released, and sex hormones are reduced to oophorectomized levels in women and orchiectomized or castrate levels in men, respectively. The development of high-dose depot formulations of GnRH agonists permitted sustained inhibition of sex steroid production and ease of drug administration.

Typically, prostate cancer is initially androgen-dependent and only in late stages becomes androgen-independent. Various methods of androgen ablation therapy were practiced, either as the only therapy or in conjunction with other treatment modalities such as surgery, external beam radiation therapy, brachytherapy, etc. A regime of high doses of the semi-synthetic estrogenic compound diethylstilbesterol was one of the earliest non-surgical options for the treatment of prostate cancer. This therapy was equally as effective in mediating remission as orchiectomy. Unfortunately, effective concentrations of the estrogenic compound caused cardiovascular complications, including edema and deep vein thrombosis. Diethylstilbesterol therapy was discontinued when GnRH agonists and antagonists became available that essentially lacked cardiovascular toxicity.

While GnRH agonists are clinically equally as effective in inducing prostate cancer remission as orchiectomy, the gold standard of treatment efficacy, their use is accompanied by important other toxicities, including fatigue, weight gain, depression, osteopenia, anemia, muscle atrophy, gynecomastia, hot flashes, loss of cognitive function, and decrease in high-density lipoprotein. Hellerstedt and Pienta. CA Cancer J Clin 2002; 52: 154-179. Perhaps, the complications that most severely affect quality of life are loss of bone mineral density and hot flashes.

Because testosterone is the main circulating sex hormone in men it was long assumed that the increased bone turnover and loss of bone mineral density in castrated men or in prostate cancer patients treated with GnRH agonists or antagonists was due to the absence of this hormone. However, recent observational studies suggested, surprisingly, that bone mineral density in men correlated better with estrogen levels than with testosterone levels. Khosla et al. J Clin Endocrinol Metab 2002 ; 87 : 1443-1450. An interventional study showed that estrogen supplementation prevented the GnRH-induced reduction in bone formation markers as well as the increase in bone resorption markers in elderly men treated with a GnRH agonist. Khosla et al. J Clin Endocrinol Metab 2001;

86 : 3555-3561. Finally, another study showed that specific inhibition of aromatase activity also resulted in a significant increase in bone resorption markers and a decrease in bone formation markers. Taxel et al. J Clin Endocrinol Metab 2002; 87 : 4907-4913.

## SUMMARY OF THE INVENTION

The invention relates to compositions comprising a first sustained release formulation of a gonadotropin hormone releasing hormone (abbreviated GnRH herein) composition capable of releasing the GnRH composition during a period of at least about one month at a rate sufficient to induce and maintain chemical castration of a male patient, and a second sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a GnRH composition that chemically castrates a male patient. Preferably, the first sustained release formulation of a composition of the invention releases a GnRH composition at a rate of between about 10 and about 1,000 µg per day. The second sustained release formulation of the invention releases an estrogenic composition under a profile comprising at least a first initial phase and a second phase. In the course of the first initial phase, the second sustained release formulation of the invention displays an attenuated initial burst. In the course of the second phase, the second sustained release formulation releases the estrogenic composition at a rate between about 10 and 100 µg of estradiol equivalent per day, preferably at a rate not exceeding about 50 µg of estradiol equivalent per day. Preferably, the release of the estrogenic composition in the course of the first initial phase never exceeds 5 times, more preferably 3 times, the upper daily release of the estrogenic composition occurring during the second phase.

In a different embodiment of the invention the composition is not limited by reference to chemical castration of a male patient. It is defined as comprising a

first sustained release formulation of a GnRH composition capable of releasing the GnRH composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day and a second sustained release formulation of an estrogenic composition capable of releasing during said period the estrogenic composition under a profile comprising at least a first initial phase and a second phase as defined above.

In the compositions of the invention the GnRH composition of the first sustained release formulation is selected from the group consisting of GnRH, agonists of GnRH, antagonists of GnRH and mixtures thereof. Preferably, the GnRH composition is a GnRH agonist selected from the group consisting of leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof. The estrogenic composition present in the second sustained release formulation is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, estradiol benzoate, estradiol cipionate, estradiol di-undecylate, estradiol enantate, estradiol hexahydrobenzoate, estradiol phenylpropionate, estradiol undecylate, estradiol valerate, estrapronicate, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, estropipate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof. In preferred compositions the GnRH composition of the first sustained release formulation is triptorelin or a salt thereof, and the estrogenic composition of the second sustained release formulation is estradiol. In most preferred compositions the GnRH composition of the first sustained release formulation is triptorelin, or a salt thereof, that is released at a rate of about 100 µg per day, and the estrogenic composition of the second sustained release formulation is estradiol that is released at a rate of between about 25 and 50 µg per day in the course of said second phase.

The invention further relates to a method for the treatment of prostate cancer, involving administration to a prostate cancer patient of a composition comprising a first sustained release formulation of a GnRH composition capable of releasing the GnRH composition during a period of at least about one month at a rate sufficient to induce and maintain chemical castration of the patient, and a second sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a GnRH composition that chemically castrates a male patient. Preferably, the first sustained release formulation of a composition administered to a prostate cancer patient releases a GnRH composition at a rate of between about 10 and about 1,000 µg per day, and the second sustained release formulation releases a estrogenic composition at a rate between about 10 and 100 µg per day. Most preferably, the second sustained release composition administered to a prostate cancer patient according to the method of the invention releases an estrogenic composition under a profile comprising at least a first initial phase, with an attenuated burst of release, and a second phase as described above.

In the compositions administered according to the method of the invention the GnRH composition of the first sustained release formulation is selected from the group consisting of GnRH, agonists of GnRH, antagonists of GnRH and mixtures thereof. Preferably, the GnRH composition is a GnRH agonist selected from the group consisting of leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof. The estrogenic composition present in the second sustained release formulation is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, estradiol benzoate, estradiol cipionate, estradiol di-undecylate, estradiol enantate, estradiol hexahydrobenzoate,

estradiol phenylpropionate, estradiol undecylate, estradiol valerate, estrapronicate, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, estropipate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof. In preferred compositions administered according to the method of the invention the GnRH composition of the first sustained release formulation is triptorelin, or a salt thereof, and the estrogenic composition of the second sustained release formulation is estradiol. In most preferred compositions of the method of the invention the GnRH composition of the first sustained release formulation is triptorelin, or a salt thereof, that is released at a rate between about 100 µg per day, and the estrogenic composition of the second sustained release formulation is estradiol that is released at a rate of between about 25 and 50 µg per day. Compositions of the invention can be administered by a subcutaneous, intramuscular, or transdermal route.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel compositions and the use of these compositions to treat hormone-responsive prostate cancer without eliciting the severe side effects characteristic of prior art hormone ablation therapies. The compositions of the invention comprise two sustained release formulations, the first comprising a gonadotropin hormone releasing hormone (GnRH) composition and the second an estrogenic composition, that are administered to a patient simultaneously. The formulations may be combined at the time of administration or may be joined at the time of manufacture. Typically, the sustained release formulations of the invention are effective for a period of at least about one month. The period of effectiveness may be as long as one year. Formulations that are even longer-lasting are considered as being within the scope of the present invention. Preferably, the compositions of the invention are designed for

treatment periods of one to three months, after which periods the compositions are re-administered.

The first sustained release formulation comprises a GnRH composition. A number of compounds were described that inhibit secretion of gonadotropins and, consequently, the secretion of androgens in men and estrogens in women. In men estrogens are derived from testosterone by the aromatase reaction. GnRH compositions include both agonists and antagonists of GnRH as well as GnRH itself. GnRH compositions of the invention may also consist of mixtures of the latter compounds. GnRH antagonists act by competing with GnRH for GnRH receptor in the pituitary gland. Normally, GnRH is secreted in a pulsating fashion. Because of the high turnover of the hormone, GnRH receptors are exposed to waves of GnRH signaling release of LH and FSH. In the presence of high concentrations of a GnRH agonist, after an initial bust of LH and FSH release, the signaling pathway is shut down through down-regulation of GnRH receptor and reduction of LH and FSH release. Within a period of several months, LH and FSH release are completely suppressed, and testosterone and estrogen concentrations reach oophorectomized levels in women and orchiectomized or castrate levels in men, respectively. In the presence of such minimal levels of testosterone and estrogen, feedback inhibition of GnRH no longer occurs. Consequently, GnRH release is maximal. This release pattern assists the maintenance of GnRH receptor down-modulation. Well-known GnRH agonists include leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histrelin, gonadorelin and salts thereof. A well-known GnRH antagonist is abarelix.

A variety of sustained release formulations of GnRH agonists were developed and are commercially available. Examples of commercial sustained release formulations of GnRH agonists include Lupron Depot 3.75 mg and Lupron Depot 7.5 mg of TAP Pharmaceuticals Inc. of Lake Forrest, IL. Lupron Depot 3.75 mg comprises 3.75 mg leuprorelin acetate, 0.65 mg gelatin, 33.1 mg DL-lactic and glycolic acids co-polymer, and 6.6 mg D-mannitol. The accompanying diluent

contains 7.5 mg carboxymethylcellulose sodium, 75 mg mannitol, 1.5 mg polysorbate 80, water, USP, and glacial acetic acid. Lupron Depot - 3 Month 22.5 mg is a formulation for intramuscular injection at three months intervals comprising 22.5 mg leuprorelin acetate in polylactide microspheres. U.S. Pat. Nos. 4,728,721; 4,849,228; 5,330,767; 5,476,663; 5,480,656; 5,575,987; 5,631,020; 5,643,607; 5,716,640; 5,814,342; 5,823,997; 5,980,488; 6,036,976. Other sustained release formulations of leuprorelin acetate include Eligard, a one-month formulation by Atrix Laboratories and Viadur, a 12-months formulation by ALZA Corporation. Zoladex 3.6 mg and 10.8 mg are one-month and three-months depot formulations, respectively, of goserelin acetate marketed by AstraZeneca. The Zoladex 3.6 mg formulation comprises goserelin acetate in an amount corresponding to 3.6 mg of goserelin in 13.3-14.3 mg D,L-lactic and glycolic acids co-polymer. Decapeptyl distributed by Ferring Corp. and Ipsen-Beaufour is a depot formulation of triptorelin acetate or pamoate. The one-month formulation of Decapetyl includes 3.75 mg triptorelin encapsulated in polylactide co-glycolide microcapsules. Similar sustained release formulations of triptorelin pamoate are distributed in the U.S. by Pharmacia/Pfizer under the name Trelstar and in Europe under the name Pamorelin. Trelstar is available as one-month or three-months sustained release formulation (Trelstar Depot 3.75 mg, Trelstar LA 11.25 mg). Trelstar Depot 3.75 mg is a sterile, lyophilized biodegradable microgranule formulation supplied as a single dose vial containing triptorelin pamoate (3.75 mg of triptorelin peptide), 170 mg poly-d,l-lactide-co-glycolide, 85 mg mannitol, 30 mg carboxymethylcellulose sodium and 2 mg polysorbate 80. For injection, the formulation is suspended in 2 ml water and injected intramuscularly. Trelstar LA 11.25 mg is a similar formulation containing triptorelin pamoate (11.25 mg of triptorelin peptide), 145 mg poly-d,l-lactide-co-glycolide, 85 mg mannitol, 30 mg carboxymethylcellulose sodium and 2 mg polysorbate 80. The formulation is suspended in 2 ml water and injected intramuscularly. Similar formulations are described in U.S. Pat. Nos. 5,134,122, 5,192,741 and 5,225,205. These patents are incorporated herein in their entirety by this reference.

Analogous sustained release formulation of GnRH, a GnRH agonist, a GnRH antagonist or mixtures thereof can be used in the compositions of the invention. Such sustained release formulations may be based on biodegradable and/or biocompatible polymers other than the polylactide-glycolide co-polymers present in the above-described commercial formulations, including ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. These and other polymers as well as methods for preparing appropriate formulations using such polymers are well known to those skilled in the art. While the first sustained release formulation of the present invention is preferably a depot formulation of triptorelin pamoate such as the Trelstar formulations, other sustained release formulations of an agonist or antagonist of GnRH, or of GnRH itself, could also be employed. Any depot formulation that continuously releases an agonist or antagonist of GnRH or GnRH at a rate sufficient to cause down-modulation of GnRH receptor and reduction of sex hormone concentrations to oophorectomized levels in women and orchiectomized or castrate levels in men, respectively, would be suitable for use with the present invention. While the exact rate of release may vary with the nature of the GnRH agonist (including GnRH) or antagonist used, the nature of the formulation, and the mode of administration, a suitable first sustained release formulation will release a GnRH agonist or antagonist at a rate of between about 10 and 1,000 µg per day.

Release of agonist or antagonist of GnRH from a first sustained release formulation will produce the well-known side effects of GnRH agonist/antagonist therapy. To counteract these side effects, in particular loss on bone mineral density and hot flashes in prostate cancer patients, the compositions of this invention comprise a second sustained release formulation that releases an estrogenic composition. Observational studies indicate that loss of bone mineral density in men may not occur if the serum level of bioavailable estradiol is at or above about 11 pg/ml. Khosla et al. J Clin Endocrinol Metab 2002; 87: 1443-1450. Taking into account the increased level of sex hormone binding globulin in

elderly men, this corresponds to a total serum estradiol level of minimally about 30 pg/ml.

Estrogenic compositions delivered by the second sustained release formulations include both natural and synthetic compounds. The preferred estrogenic composition is estradiol (chemical name: β-estra-1,3,5(10)-triene-3,17-diol; CAS RN: 50-28-2). Examples of other estrogenic compositions that can be used according to the present invention include chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol benzoate, estradiol cipionate, estradiol di-undecylate, estradiol enantate, estradiol hexahydrobenzoate, estradiol phenylpropionate, estradiol undecylate, estradiol valerate, estrapronicate, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, estropipate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, and mixtures thereof. Because the potencies and pharmacokinetic properties of these estrogenic compositions are widely different, amounts of such estrogenic compositions to be used and concentrations to be reached will vary widely. For the purposes of this invention, amounts and concentrations of estrogenic compositions are defined by their equivalence to amounts and concentrations of estradiol. Equivalence means similarity of desirable biological effects achieved, e.g., reduction in loss of bone mineral density and/or reduction in frequency and severity of hot flashes in prostate cancer patients undergoing hormone ablation therapy.

Additional estrogenic compositions include estrogen receptor modulators (SERM) such as tamoxifen, toremifene, raloxifene, tibolone and lasofoxifene. Riggs & Hartman, 2003. N Engl J Med 348, 618-629. Ke et al. 2001. J Bone Miner Res 16, 765-773. Because of the selectivity of these compositions, their use in a second sustained release formulation of this invention may only produce some but not all of the beneficial effects resulting from estradiol administration.

For example, raloxifene, toremifene and tamoxifen can be expected to slow bone resorption but not to reduce (but, possibly, to enhance) the incidence and severity of hot flashes. Estrogenic compositions also include so-called ANGELS (Activators of Non-Genotropic Estrogen-like Signaling) compounds that were described in patent application PCT/US02/18544. ANGELS compounds are small molecules that mimic the non-genotropic effects of estrogen and androgen but substantially lack their genotropic effects. A preferred ANGELS compound is (3α,17β)-estr-4-ene-3,17-diol (CAS RN: 35950-87-9) that was shown to reverse bone loss in mouse models. Kousteni et al. 2002. Science 298, 843-846.

Estrogens are well known to increase the probability of cardiovascular events, in particular edema and deep venous thrombosis. This realization was an important reason why diethylstilbesterone therapy was abandoned for GnRH agonist therapies. Analogous observations were made for estrogen replacement therapies for postmenopausal women. Although the toxicity of estrogens to prostate cancer patients may be mitigated to some extent if the route of administration of the hormone is changed from oral to parenteral, there still may be a significant remainder risk associated with the administration of elevated doses of estrogens. To effectively counteract the negative side effects of GnRH administration without unnecessarily increasing the risk associated with high levels of estrogens, the second sustained release formulation releases an estrogenic composition at a low rate that is calculated to be only sufficient to provide a serum estrogen level equivalent to about 30 pg/ml of estradiol. Because of biological differences between subjects, the actual serum estradiol or estradiol equivalent level achieved by administration of the second sustained release formulation may vary between about 10 pg/ml and about 30 pg/ml. Sustained release formulations almost inevitably show a bimodal kinetics of drug release, comprising an initial burst of release that is followed by a prolonged phase of sustained release at a considerably lower rate. A preferred second sustained release composition of this invention displays a release profile that approaches unimodality. Because of the absence of an important initial burst of

drug release from this second sustained release formulation, estrogen concentrations will never greatly exceed target levels. The calculated ideal rate of release of estrogenic composition is equivalent to about 25 µg/day of estradiol (clearance x desired serum level or increase in serum level). The maximal rate of release of estrogenic composition during the first days following administration of the second slow release formulation will be equivalent to about 75 µg estradiol per day. As a consequence of these narrowly defined release characteristics of the second sustained release formulation, the risk associated with a high estrogen level will be kept to a minimum.

## DESCRIPTION OF SECOND SUSTAINED RELEASE FORMULATION

The second sustained release formulation has been prepared according to one of the following Examples.

Example 1 :

9.8 g of polymer 50:50 poly (D,L-lactide-co-glycolide) (inherent viscosity (iv) = 0.5 dl/g) are dissolved in 60g of methylene chloride under magnetic agitation. 200 mg of estradiol are dispersed in the polymer solution under magnetic stirring. 5 ml ethanol are added drop wise to the mixture to dissolve the active ingredient. The solvent is then partially evaporated under reduced pressure, until reaching an adequate consistency. The resulting mixture is flown on a Teflon piece and the film is dried under reduced pressure at room temperature for minimum 12 h. Afterwards, the film is cut and extruded on a press extruder fitted with a 3 holes die at a temperature of 75°C. The extrudates are cut, frozen with liquid nitrogen and ground on a 500 µm ring.

Exemple 2:

The aqueous phase (Solution A) is prepared by mixing under magnetic agitation 10 g of PVA (polyvinyl alcohol) and 1990 g $H_2O$ MilliQ at a temperature of 40°C. Next, the organic phase (Solution B) is prepared by dissolving 4.9 g of polymer 50:50 poly (D,L-lactide-co-glycolide) (inherent viscosity (iv) = 0.5 dl/g) in 25 g of ethyl acetate under magnetic agitation. 100 mg of estradiol are dissolved in 800 µl of DMSO (solution C). Solutions B and C are mixed and this solution is pumped through a needle into the homogenization chamber at a rate of 5 ml/minute. Solution A is pumped in parallel at a rate of 600 ml/minute into the homogenization chamber. The rotation speed of the rotor is 5500 rpm and the process lasts about 6 minutes. The suspension thus obtained is filtered on 1.2 µm and the particles are then recuperated by filtration followed by lyophilization (60 min at –40°C, 960 min at 25°C, 121 min at 30°C, finish at 25°C).

Example 3 :

The following procedure was used to encapsulate estradiol in poly(lactide-co-glycolide) polymer using the biocompatible solvent ethyl acetate. First, a polymer solution was prepared by dissolving 3.92 g of poly(D,L-lactide-co-glycolide) 50:50 (i.v. = 0.34) in 28.46 g of ethyl acetate. Next, 0.08 g of estradiol was dissolved in 30.0 g of ethyl acetate. A stirrer was fitted with a 6-bladed steel impeller. A 250 ml glass beaker was positioned below the impeller such that the impeller was 1 cm above the bottom of the beaker. Next, the polymer and estradiol solutions were transferred to the 250 ml beaker and agitated at 700 rpm. Using a peristaltic pump, 103.5 g of silicon oil (Dow Corning 360 Medical Fluid) having a viscosity of 350 cs, was added to the polymer/estradiol solution at a rate of 8 g/minute. Upon addition of the non-solvent, silicone oil, the polymer and estradiol separated in the form of soft microspheres that remained suspended due to force of the impeller. Separately, 1000 g of volatile silicone fluid (boiling point : 205º) was placed in a 2 l beaker. A stirrer (Janke & Kunkle) was fitted with a 4-bladed steel impeller. The impeller was placed in the silicone fluid and the fluid was

stirred. The suspension of soft microspheres was poured into the beaker containing silicone fluid and stirred at 700 rpm for 45 minutes. The hard microspheres were collected by filtration and rinsed with 50 ml of hexane. The microspheres were vacuum dried at room temperature.

## CLAIMS

1. A composition comprising:

a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition during a period of at least about one month at a rate sufficient to induce and maintain chemical castration of a male patient, and

a sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a gonadotropin hormone releasing hormone composition that chemically castrates a male patient.

2. The composition according to claim 1, wherein the sustained release formulation of a gonadotropin hormone releasing hormone composition is capable of releasing the gonadotropin hormone releasing hormone composition at a rate between about 10 and about 1,000 µg per day.

3. The composition according to claim 1, wherein the sustained release formulation releases an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the daily release of the estrogenic composition occurring during said second phase.

4. A composition comprising:

a sustained release formulation of a gonadotropin hormone releasing

hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day and

a sustained release formulation of an estrogenic composition capable of releasing the estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

5. The composition according to any of the preceding claims, wherein the gonadotropin hormone releasing hormone composition is selected from the group consisting of gonadotropin hormone releasing hormone, agonists of gonadotropin hormone releasing hormone, antagonists of gonadotropin hormone releasing hormone and mixtures thereof.

6. A composition as in claims 1, 2, 3 or 4, wherein the gonadotropin hormone releasing hormone composition is a gonadotropin hormone releasing hormone agonist selected from the group consisting of leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof.

7. A composition as in claims 1, 2, 3 or 4, wherein the estrogenic composition is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, estradiol benzoate, estradiol cipionate, estradiol di-undecylate, estradiol enantate, estradiol

hexahydrobenzoate, estradiol phenylpropionate, estradiol undecylate, estradiol valerate, estrapronicate, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, estropipate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof.

8. A composition as in claims 1, 2, 3 or 4, wherein the gonadotropin releasing hormone composition is triptorelin or a salt thereof and the estrogenic composition is estradiol.

9. The composition of claim 8, wherein triptorelin, or a triptorelin salt, is released at a rate of about 100 µg per day and estradiol is released at a rate between about 25 and 50 µg per day.

10. A method for the treatment of prostate cancer comprising:

Administering to a patient suffering from prostate cancer a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at a rate sufficient to induce and maintain chemical castration of the patient, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition capable of maintaining for said period a serum level sufficient to reduce the enhanced loss of bone mineral density or the hot flashes that are normally caused by the administration of a gonadotropin hormone releasing hormone composition that chemically castrates a male patient.

11. A method for the treatment of prostate cancer comprising:

Administering to a patient suffering from prostate cancer a sustained

release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

12. A method for the treatment of prostate cancer comprising:

Administering to a patient suffering from prostate cancer a sustained release formulation of a gonadotropin hormone releasing hormone composition capable of releasing the gonadotropin hormone releasing hormone composition for a period of at least about one month at an average rate between about 10 and 1,000 µg per day, and

Simultaneously administering to the patient a sustained release formulation of an estrogenic composition under a profile comprising at least a first initial phase and a second phase, the release of the estrogenic composition in the course of said second phase being at a rate between about 10 and 100 µg of estradiol equivalent per day, the release of the estrogenic composition in the course of said first initial phase never exceeding 5 times the upper daily release of the estrogenic composition occurring during said second phase.

13. A method as in claims 10, 11 or 12, wherein the gonadotropin hormone releasing hormone composition is selected from the group consisting of gonadotropin hormone releasing hormone, agonists of gonadotropin hormone releasing hormone, antagonists of gonadotropin hormone releasing hormone and mixtures thereof.

14. A method as in claims 10, 11 or 12, wherein the gonadotropin hormone releasing hormone composition is a gonadotropin hormone releasing hormone agonist selected from the group consisting leuprorelin, goserelin, triptorelin, buserelin, nafarelin, deslorelin, histerelin, gonadorelin, and salts and mixtures thereof.

15. A method as in claims 10, 11 or 12, wherein the estrogenic composition is selected from the group consisting of chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol dipropionate, diethylstilbestrol monobenzyl ether, equilelinin, equilelinin sulfate, estetrol, estradiol, estradiol benzoate, estradiol cipionate, estradiol di-undecylate, estradiol enantate, estradiol hexahydrobenzoate, estradiol phenylpropionate, estradiol undecylate, estradiol valerate, estrapronicate, (3α,17β)-estr-4-ene-3,17-diol, estriol, estriol hemisuccinate, estrone, estrone sulfate monosodique, estrone potassium sulfate, estropipate, ethinylestradiol, fosfestrol tetrasodique, hexestrol, hydroxyestrone diacetate, mestranol, pinestrol, piperazine estrone sulfate, promestriene, quinestrol, tamoxifen, toremifene, raloxifene, lasofoxifene and mixtures thereof.

16. A method as in claims 10, 11 or 12, wherein the gonadotropin releasing hormone composition is triptorelin or a salt thereof and the estrogenic composition is estradiol.

17. A method according to claim 16, wherein triptorelin, or a triptorelin salt, is released at a rate of about 100 µg per day and estradiol is released at a rate between about 25 and 50 µg per day.

18. A method as in claims 10, 11 or 12, wherein the composition is administered by a subcutaneous, intramuscular, or transdermal route.

## ABSTRACT

The present invention relates to compositions comprising two sustained release formulations, the first being capable of releasing a gonadotropin releasing hormone composition and the second an estrogenic composition. The compositions of the invention can be employed for an improved androgen deprivation therapy of prostate cancer, in which therapy loss of bone mineral density and the occurrence and severity of hot flashes are minimized through the maintenance of a minimally adequate estrogen level.

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